Fortnightly review

Hypothyroidism: screening and subclinical disease

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At first sight there could hardly be a more simple disorder to diagnose and treat than hypothyroidism. Now that we have robust hormone assays and reliable preparations of thyroxine in tablet sizes sufficiently small to tailor doses to an individual's requirement, what issues remain? The purpose of this review is to flesh out some of the recently published consensus views on hypothyroidism,[1 2] in particular regarding the role of screening for hypothyroidism and the need for treatment in subclinical hypothyroidism. Table 1 gives the definitions of hypothyroidism.

Summary points

- Subclinical hypothyroidism is common, especially in elderly women
- The presence of subclinical hypothyroidism or thyroid antibodies increases the risk of developing overt hypothyroidism and the risk is even greater (about 5% a year) if both are present together
- Thyroid stimulating hormone concentrations above 2 mU/l are associated with an increased risk of hypothyroidism
- Screening all acutely ill patients or the healthy general population for hypothyroidism is not recommended
- Case finding, especially in women over 40 with non-specific symptoms, is currently the best approach to detect previously unsuspected hypothyroidism
- Modest symptomatic benefits occur with thyroxine treatment in some patients with subclinical hypothyroidism, and lipid profiles may also improve
- Monitored thyroxine treatment, maintaining normal thyroid stimulating hormone concentrations, has no adverse effects

Methods

I have conducted a monthly Medline search for all articles on hypothyroidism for five years. For this review I scanned these papers and background papers for a recent consensus statement,[2] together with their references, for those focusing on screening and subclinical hypothyroidism. In addition, as part of my 15 years of thyroid related research I have continuously reviewed the literature.

Frequency of hypothyroidism

New information on the frequency of hypothyroidism has been provided by a survey of a randomly selected population of 2779 adults living in Whickham, Tyne and Wear, who had baseline thyroid function tests and were then reexamined after 20 years.[3] Remarkably, 96% of the 1877 survivors participated in a follow up survey and 91% had further tests. The mean incidence of spontaneous overt hypothyroidism in women was 3.5 survivors/1000/year and in men 0.6/1000/year. There was no apparent excess of hypothyroidism in those who had died. The mean average at diagnosis was 58-59, but the probability of developing hypothyroidism increased steadily with age, reaching 14 cases/1000/year for women aged 75-80.

This survey also clarified the predictive value of detecting thyroid antibodies (against thyroid peroxidase/microsomal antigen) and measuring thyroid stimulating hormone concentrations. For women with subclinical hypothyroidism but without thyroid antibodies the relative risk of developing overt hypothyroidism over the follow up period was 8; the risk was the same for those with thyroid antibodies and normal thyroid stimulating hormone concentrations. Women with both increased thyroid stimulating hormone concentrations and thyroid antibodies had a relative risk of 38. Relative risks were even higher in men. Furthermore, even within the reference range of around 0.5-4.5 mU/l, a high thyroid stimulating hormone concentration (>2 mU/l) was associated with an increased risk of future hypothyroidism (fig 1). The simplest explanation is that thyroid disease is so common that many people predisposed to thyroid failure are included in a laboratory's reference population, which raises the question whether thyroxine replacement is adequate in patients with thyroid stimulating hormone levels above 2 mU/l. The high frequency of overt and subclinical hypothyroidism observed raises another contentious issue—namely, whether screening for hypothyroidism is worth while.

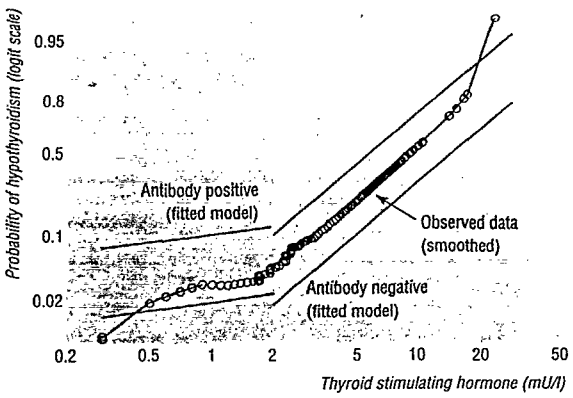

Fig 1 Logit probability (log odds) for the development of hypothyroidism in women during a 20 year follow up of 912 women.[3] Reproduced with permission

Screening for hypothyroidism

General population screening

Screening for congenital hypothyroidism is definitely worth while as it is relatively common (1:4000 births), the test is sensitive and specific (thyroid stimulating hormone measurement in heel prick specimens), it has serious consequences if untreated (brain damage), and effective treatment is available (thyroxine). However, screening for hypothyroidism in hospital patients is not effective.[4,5] Although undiagnosed hypothyroidism is more common in adults than neonates, the non-specific effects of acute illness on thyroid function tests often produce abnormal results which correct themselves after recovery. The best current recommendation is to maintain a low threshold for suspecting hypothyroidism, particularly in its more obscure presentations, and to reserve testing for these patients.[5]

In apparently healthy people routine screening is generally not recommended, even in those over 60 and with a family history of thyroid disease.[2,4] Reasons for this include a relatively low point prevalence of overt disease and uncertainty over the benefits of detecting subclinical hypothyroidism (see below). However, a cost utility analysis using a computer decision model to assess the consequences and costs of thyroid stimulating hormone screening recently came to the conclusion that testing 35 year old men and women, with repeat estimates every five years for 50 years, would be beneficial.[6]

Table 1 Definitions of hypothyroidism

	Thyroid stimulating hormone	Thyroxine	Symptoms
Subclinical hypothyroidism:	Raised	Normal	Usually absent; some authorities require the absence of symptoms as a criterion and use the term mild hypothyroidism for subclinical hypothyroidism plus symptoms
Grade 1*	Above upper limit of *reference range* (≤10 mU/l)	Normal	
Grade 2	10.1-20 mU/l	Normal	
Grade 3	>20 mU/l	Normal	
Clinical or overt hypothyroidism:	Raised	Low	Usually present; symptoms are not considered a criterion by some authorities

*Symptoms are increasingly likely with higher thyroid stimulating hormone concentrations.

The cost of detecting subclinical hypothyroidism was $9223 (£6148) for women and $22 595 (£15 063) for men per quality adjusted life year.[6] Most of the quality adjusted life years (52%) were accounted for by preventing progression to overt hypothyroidism and 30% by improving associated mild symptoms; 2% were estimated to be due to prevention of cardiovascular disease through the effect of hypothyroidism on cholesterol concentrations. This last estimate may be too high as the 20 year Whickham survey found no evidence of increased mortality or ischaemic heart disease in women with thyroid antibodies or raised thyroid stimulating hormone concentrations.[7]

Another assumption in the model was that only those patients with subclinical hypothyroidism plus thyroid antibodies are at risk of progression to overt hypothyroidism. Since raised thyroid stimulating hormone alone is a predictor of overt hypothyroidism, more cases at risk will be ascertained (which in turn will alter costs). Nevertheless, the final conclusion was that screening for hypothyroidism is as favourable as screening for hypertension in the same age group, providing a similar increase in quality adjusted days. It is also important to note that screening based on thyroid stimulating hormone concentrations will of course also turn up subclinical and overt thyrotoxicosis,[8] and arguably this is even more important to recognise and treat.

Further analyses based on existing local screening schemes are therefore needed to determine the true place of thyroid stimulating hormone testing for the general population. At present the benefits remain debatable. One reasonable alternative is the case finding approach, focusing testing on patients visiting their doctors for an unrelated reason; this is particularly effective in women over 40 with non-specific symptoms.[4]

Screening in special groups

Hypothyroidism occurs after all types of treatment for hyperthyroidism, and patients who are euthyroid should be offered annual screening by means of a computerised register (box).[2] Patients taking lithium or amiodarone are at risk of hypothyroidism and thyrotoxicosis and need regular monitoring of thyroid function.[2]

There is no consensus on the place of screening for postpartum thyroiditis.[9] However, women with insulin dependent diabetes mellitus are three times more likely to develop postpartum thyroid dysfunction than non-diabetic controls and may have unsuspected thyroid disease in pregnancy.[10] Ideally, all diabetic women should have thyroid antibody measurements in the first trimester, with careful follow up of those with positive results. Also, any woman who develops postpartum thyroiditis should be offered annual follow up, as about a quarter of these women will develop overt hypothyroidism within the next five years.[11]

Some psychiatric disorders may be exceptions to the rule that acutely ill patients should only be tested for hypothyroidism if there is clinical suspicion, in particular bipolar affective disorder with rapid cycling[12] and refractory depression.[13] The effect of thyroid treatment in these conditions is still uncertain. Delaying testing until the third week after admission avoids the transient disturbances due to the effects of acute psychiatric illness.[14] Although frequently sought in dementia, unsuspected hypothyroidism is rare.[4] There is an unexplained

association between breast cancer and autoimmune (Hashimoto's) thyroiditis, with a threefold increase in the prevalence of thyroid antibodies, and it may be worth screening such patients for thyroid dysfunction.[15]

Treatment of subclinical hypothyroidism

A big argument in favour of screening is that recognition and treatment of subclinical hypothyroidism is beneficial.[6] At first sight this seems paradoxical because free thyroxine concentrations are normal and some regard the exclusion of symptoms as a criterion for diagnosis (table 1).[2 8] However, many patients do have non-specific symptoms, such as tiredness and weight gain, which could be due to hypothyroidism. After all, the thyroid function tests needed to establish the biochemical diagnosis have usually been performed because of this suspicion. Also, after treatment with thyroxine the patient may notice an improvement in symptoms previously unrecognised because of the slow progression of thyroid failure and its variable manifestations. As thyroid stimulating hormone concentrations above 2 mU/l reflect a disturbance of the thyroid-pituitary axis (fig 1), values above the upper level of the typical reference range (4.5 mU/l) are highly significant departures from normal rather than one tail of the normal distribution. Is there any hard evidence that these patients benefit from early treatment?

Effect on neuropsychiatric and other symptoms

One small crossover trial has indicated that thyroxine improves symptom scores (including mental lethargy) and psychometric performance compared with a placebo.[16] This trial is supported by a study which included patients previously treated for hyperthyroidism[17] and by a prospective, unblinded trial of thyroxine in patients with subclinical hypothyroidism.[18] More tenuous is the evidence that subclinical hypothyroidism is common in affective disorders, as such observations have been uncontrolled or the effects of thyroxine replacement have not been assessed.[19-21]

Postpartum symptoms of depression are more common in women who have thyroid antibodies than in those without irrespective of biochemical thyroid dysfunction.[22] Also, in patients with rapid cycles of a bipolar affective disorder the most significantly associated thyroid disorder was thyroid antibody positivity and not raised thyroid stimulating hormone concentration.[12] Whatever the reason, the implication is that some mood disturbance in subclinical hypothyroidism has an immunological rather than an endocrinological basis, in which case thyroxine treatment would not help.

Effect on lipids

The adverse effects of subclinical hypothyroidism on cholesterol concentrations have been promoted as a reason for screening and treatment.[6 23] A recent study found an association of subclinical hypothyroidism not only with raised low density lipoprotein cholesterol and low high density lipoprotein cholesterol concentrations but also with raised lipoprotein(a).[24] Although hypothyroidism theoretically increases the risk of cardiovascular disease, there is no evidence that thyroxine will reverse this potential and, indeed, any such risk must be small, given the results from the Whickham survey.[7] The effects of thyroxine replacement on cholesterol lowering alone are modest. A re-analysis of intervention studies between 1976 and 1995 led to the following conclusions[25]:

- Subclinical hypothyroidism is two to three times more common than expected in people with increased total plasma cholesterol concentrations
- Total cholesterol is only slightly raised (0-30% above normal) in subclinical hypothyroidism.

Indications for screening for hypothyroidism

Established	Turner's syndrome; Down's syndrome
Congenital hypothyroidism	Autoimmune Addison's disease
Treatment of hyperthyroidism	**Uncertain**
Neck irradiation	Breast cancer
Pituitary surgery or irradiation	Dementia
Patients taking amiodarone or lithium	Patients with a family history of autoimmune thyroid disease
Probably worth while	Pregnancy, looking for postpartum thyroiditis*
Type 1 diabetes antepartum*	Obesity
Previous episode of postpartum thyroiditis	Idiopathic oedema
Unexplained infertility	**Not indicated**
Women over 40 with non-specific complaints	Acutely ill patients with no clinical reason to suspect thyroid disease
Refractory depression; bipolar affective disorder with rapid cycling	

*Check thyroid antibodies; screen positive patients post partum using thyroid stimulating hormone.

Other effects

Minor alterations in heart muscle contractility, determined by systolic time intervals, occur in around half of patients, although not all studies agree.[8] Only a subgroup with the most serious abnormalities improves with thyroxine replacement.[17] An asymptomatic polyneuropathy can be identified in subclinical hypothyroidism,[26] but the response to treatment has not been analysed and the clinical impact of this is even less clear than for alterations in myocardial function. One potentially important adverse effect of subclinical hypothyroidism is to alter the dynamics of prolactin release, with unknown consequences for gonadal function and fertility.[27] Testing for thyroid disease seems warranted in all women and men with unexplained infertility.

Another argument in favour of instituting thyroxine replacement is that it prevents the onset of overt hypothyroidism. This is particularly persuasive for people with raised thyroid stimulating hormone concentrations plus thyroid antibodies, who have an annual risk of developing overt hypothyroidism of around 5%.[3] Practically, however, the patient is probably not spared many follow up visits in return for starting thyroxine early. This is because thyroxine dose requirements are less in subclinical hypothyroidism than in overt disease, and so careful monitoring is needed until the normal replacement dose is reached (100-150 µg daily). At this time checks every one to three years can be instituted, provided that thyroid stimulating hormone concentrations are normal and stable.

Disadvantages of treatment

Are there risks from taking thyroxine which argue against treating subclinical hypothyroidism? Providing thyroid stimulating hormone concentrations are restored to the reference range, the answer is no, and

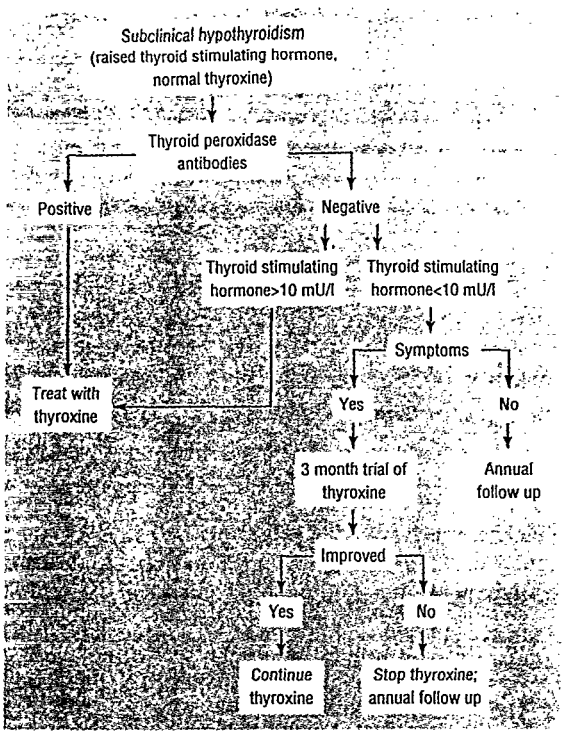

Fig 2 Algorithm for managing non-iatrogenic subclinical hypothyroidism. Thyroid peroxidase antibodies alone are recommended for screening as thyroglobulin antibodies rarely occur in the absence of these antibodies[2]

even if too much is given, the risks of osteoporosis are more theoretical than real. A meta-analysis of studies of excessive thyroxine treatment found no reduction in bone mass in premenopausal women, although postmenopausal women had a significant excess annual bone loss of 0.9%/year after 10 years.[28] However, no increased rate of fractures occurs, despite this loss, and it is also important to distinguish those who are taking thyroxine for iatrogenic hypothyroidism from those with spontaneous hypothyroidism: in the first group there has usually been a period of hyperthyroidism which contributes to the bone loss.[29]

The other main concern is the action of excessive thyroxine on the heart. Subclinical hyperthyroidism in people aged 60 or older is associated with a trebling of the risk of atrial fibrillation over 10 years.[30] It is not clear whether the risk applies equally to patients taking thyroxine for iatrogenic hypothyroidism and those with spontaneous hypothyroidism. This study is the most persuasive reason to maintain normal thyroid stimulating hormone concentrations in all patients receiving thyroxine, whether for subclinical or overt hypothyroidism. On balance, the risks of properly monitored thyroxine treatment are almost non-existent.

Conclusions

Clinical and subclinical hypothyroidism are common. The presence of either a raised thyroid stimulating hormone concentration or thyroid antibodies indicates an increased risk of future hypothyroidism and this is greater when both occur together. Screening for hypothyroidism may be more cost effective than usually presumed and certain subgroups at risk can be identified, but further work is needed to establish the optimum strategy. On the other hand, the high frequency of abnormal thyroid function test results in acutely ill patients means that any testing should be reserved for those in whom there is clinical suspicion of thyroid dysfunction. There are modest benefits from treating subclinical hypothyroidism, and figure 2 suggests a management strategy.

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